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HORMETIC EFFECTS OF REACTIVE OXYGEN SPECIES BY EXERCISE: A VIEW FROM ANIMAL STUDIES FOR SUCCESSFUL AGING IN HUMAN

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□ Numerous anti-aging measures have been proposed to cope with age-associated decline of physiological functions and/or onset of diseases, mostly based on free radical (or oxidative stress) theory of aging, though no robust scientific data have been reported to extend human healthspan. This is due to dual (harmful as well as essential) roles of reactive oxygen species (ROS) to a body. Regular moderate exercise provides benefits upregulating defense against oxidative stress in good balance between the opposing dual roles. Sources of ROS in exercise appear to be not only mitochondria as often claimed but also enzymatic reactions catalyzed by NADPH oxidase and other oxidases. It may, therefore, be possible to mimic this aspect of exercise to promote the defense for healthspan extension by other means such as modest alcohol consumption that could upregulate activity of enzymes against oxidative stress.

Keywords: exercise, hormesis, reactive oxygen species, anti-oxidant, healthspan

INTRODUCTION

Despite remarkable prolongation of lifespan in developed countries in the last several decades, a considerable proportion of the elderly population is frail and vulnerable to physical and mental disorders that impairs quality of their later lives. Numerous anti-aging measures have been proposed to ameliorate and/or retard age-associated decline of physiological functions and/or onset of diseases. A most popular working hypothesis on mechanisms of aging, free-radical theory of aging/oxidative stress theory of aging (Harman 2009), has been the basis of major anti-aging strategies, although the theory has been criticized as being not definitely proven (Muller et al. 2007). In accordance with such claims, anti-oxidants including vitamin C and E have been used by people with little or no health promoting effects except in obvious disease conditions in an attempt to reduce damage due to reactive oxygen species (ROS) that may drive aging and cause diseases. These vitamins and anti-oxidants such as catechins and other polyphenols can even be detrimental to ani-

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mals and human (Bjelakovic *et al.* 2008). These facts, however, are not necessarily contradictory to the oxidative theory of aging in view of possible hormetic effects of ROS.

OPPOSING ROLES OF ROS AND CRITIC OF USING ANTI-OXIDANTS TO REDUCE OXIDATIVE STRESS

ROS are generated in a variety of cellular processes. Superoxide anion radicals are byproducts of electron transport system in mitochondria and endoplasmic reticulumn. Chemical reactions catalyzed by oxidases such as NADPH oxidase, xanthine oxidase and monoamine oxidase produce superoxide and/or hydrogen peroxide as normal and inevitable products. Highly reactive hydroxyl radicals generated from hydrogen peroxide by transition metal catalyzed Fenton reaction can damage proteins, nucleic acids and membrane phospholipids. On the other hand, it has been clearly demonstrated that superoxide and/or hydrogen peroxide have essential physiological roles in cellular functions such as signal transduction, cell proliferation and transcription regulation (Droge 2002). Because of such opposing roles of ROS, anti-oxidants often claimed to reduce oxidative stress have been criticized as having no significant effects or potentially detrimental consequences.

EXERCISE HORMESIS AND POSSIBLE HUMAN HEALTHSPAN EXTENSION BY MODERATE OXIDATIVE STRESS

Extensive physical activities in unprepared body can cause oxidative damage of nucleic acids, proteins and membrane lipids in various tissues (Davies et al. 1982) due to massive generation of ROS. ROS are generated during and/or after exercise in mitochondrial respiratory chain, and reactions catalyzed by monoamine oxidase (Cadenas and Davies 2000), NADPH oxidase or myeloperoxidase in neutrophils mobilized or infiltrated in the skeletal muscle (Peake and Suzuki , 2004), xanthine oxidase (Viña et al.2000) as well as from endotherial cells in vascular systems (Rush and Aultman 2008). It should be noted that ROS generation from respiring mitochondrial is claimed to be one or two orders of magnitude lower than reported (i.e., 2 to 3 % of oxygen consumed) in the skeletal muscle and liver under conditions that mimic physiological situations (St-Pierre et al. 2002). Major sites of ROS generation are not only mitochondria but also other sources such as xanthine oxidase and NADPH oxidase catalyzed reactions (Bonetto et al. 2009). Hypoxia-induced generation of ROS can also be an important source (Clanton 2007). Due to massive consumption of oxygen in the skeletal muscle during exercise, transient lowering of oxygen concentration may result in other tissues, thus causing temporary local hypoxia. It is, therefore, likely that modest increase of ROS by exercise can induce defense enzymes and other proteins

against oxidative stress systemically in cells and tissues unprepared for excessive generation of ROS. Such situations would lead to adaptation to stronger stress that may be encountered in future.

Indeed, we have shown that regular swimming exercise in young and middle-aged rats can reduce protein carbonyls in the brain that are accompanied with upregulation of the activity of proteasome for degradation of the oxidatively modified proteins (Radák et al. 2001). Similarly, regular treadmill running reduced oxidative damage to DNA in the skeletal muscle (Radák et al. 1999) and liver (Nakamoto et al.2007) of aged rats, with the increase in the repair enzyme activity (OGG1). Higher protection against oxidative stress was also observed in the myocardium after regular swimming exercise (Radák et al. 2000). It was also demonstrated that regular treadmill running apparently attenuated age-associated increase in oxidative stress by reducing NF-kB activation with increased level of reduced form of glutathione in the liver of aged rats (Radak et al.2004). Others have reported upregulation of antioxidant enzymes by exercise (e.g., Ji et al, 2006). Thus, mild oxidative stress induced by exercise appears to be able to reduce oxidative damage by upregulating antioxidant systems, collectively termed as primary (e.g. glutathione), secondary (e.g. glutathione peroxidase) and tertiary (e.g. OGG1 and proteasome) defense system. As such, we have argued that dual (harmful and beneficial) effects of ROS generated by exercise can be a form of hormesis (Radák et al.2005, 2008; Ji et al.2008). Supporting this argument, we have shown that hydrogen peroxide (oxidant) or N-tert butyl-alpha-phenyl nitrone (anti-oxidant) injection modulates neurotrophin levels in the spinal cord in rats, apparently via alteration of redox state (Siamilis et al.2009).

In agreement with the idea of exercise hormesis caused by ROS in animals, human studies of antioxidant supplementation have been reported to attenuate beneficial effects of exercise. Khassaf et al. (2003) found that long term vitamin C supplementation attenuated adaptive response of exercise to oxidants in human lymphocytes. Fischer et al. (2004) reported that supplementation of vitamin C and E blunted exercise induced IL-6 release from contracting human skeletal muscle. More recently, Ristow et al. (2009) demonstrated that health promoting effects of physical exercise such as upregulation of glucose infusion rate, plasma adiponectin level and mRNA of anti-oxidant enzymes in human skeletal muscle are abolished by administration of vitamin C and E.

Thus, ROS generated by physical activity appears to upregulate defense against oxidative stress and other beneficial effects in both rodents and humans. It is, therefore, likely that mild oxidative stress is useful in retarding physiological decline and reducing risk of diseases associated with aging whether it is caused by exercise or perhaps by other means (see below).

CONCLUSION AND PERSPECTIVES

Obviously, too much physical activity is harmful due to massive generation of ROS, if a body is not conditioned to minimize damage. Modest and regular exercise, however, can induce cellular defense against stronger oxidative stress, promoting health and reducing risk of diseases. Importantly, such hormetic adaptation can occur even at old ages at least in model animals (Goto et al.2004; Cui et al.2009). It has not been demonstrated whether it is true in older humans as has been shown in young individuals as cited above. It is interesting to point out that alcohol consumption, if modest, promotes health despite it causes oxidative stress. Notably, prior intake of alcohol can attenuate ischemic/reperfusion damage in the brain in model animals due to ROS generation in NADPH oxidase catalyzed reaction (Wang et al. 2007). Thus, moderate alcohol intake can have hormetic effects similar to exercise via ROS generation. Lipopolysaccharide (LPS), a bacterial endotoxin that induces inflammation, activates NADPH oxidase dependent ROS production from neutrophils (Brandes et al.1999). LPS might also be viewed as an agent that could cause beneficial outcomes if doses would not be high, as in the case of non-severe bacterial infection, thereby possibly promoting anti-oxidant defense. It would be interesting to explore means for mild oxidative stress such as those suggested in the effect of polyphenols as prooxidants that can induce defense against stronger harmful stress, rather than reducing oxidative stress by their antioxidant activity *per se* (Stevenson and Hurst 2007).

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